Epidemiol. Infect. (2015), **143**, 725–733. © Cambridge University Press 2014
doi:10.1017/S0950268814001204

High incidence of norovirus GII.4 outbreaks in hospitals and nursing homes in Catalonia (Spain), 2010–2011

P. GODOY[1,2]*, G. FERRRUS[1], N. TORNER[1,2,7], N. CAMPS[1], M.R. SALA[1], S. GUIX[3,4], R. BARTOLOMÉ[5], A. MARTÍNEZ[1], M. DE SIMÓN[6], A. DOMÍNGUEZ[2,7] and the Working Group for the Study of Outbreaks of Acute Gastroenteritis in Catalonia†

[1] *Department of Health, Generalitat of Catalonia, Spain*
[2] *CIBER Epidemiología y Salud Pública (CIBERESP), Spain*
[3] *Enteric Virus Group, Department of Microbiology, University of Barcelona, Spain*
[4] *Nutrition and Food Safety Research Institute (INSA-UB), University of Barcelona, Spain*
[5] *Microbiology Service, Vall d'Hebron Hospital, Catalonia, Spain*
[6] *Public Health Agency of Barcelona, Spain*
[7] *Department of Public Health, University of Barcelona*

Received 6 February 2014; Final revision 15 April 2014; Accepted 23 April 2014; first published online 27 May 2014

SUMMARY

A descriptive study was performed between 1 January 2010 and 31 December 2011 to estimate the incidence of norovirus outbreaks in hospitals and nursing homes in Catalonia (Spain). Epidemiological surveys were done for each outbreak. Norovirus was confirmed using RT–PCR. The incidence of outbreaks/10^6 person-years by centre, and the attack rate, were calculated. Statistically significant differences were calculated using odds ratio (ORs) and 95% confidence intervals (CIs). Person-to-person transmission was responsible for 81·5% (22/27) of outbreaks. The incidence in the population was 156·7 outbreaks/10^6 person-years. The incidence by centre was 1·3% per year and was greater in hospitals (2·6%) than in nursing homes (0·9%) (OR 3·2, 95% CI 1·5–6·9). The global attack rate in residents and staff was 34·7% (816/2348). The mortality rate was 0·25% (2/816). Genogroup GII.4 caused 66·7% of outbreaks. Norovirus GII.4 outbreaks cause significant morbidity affecting both patients and staff.

Key words: Epidemiology, hospitals, norovirus, Norwalk-like virus, nursing home, outbreak.

INTRODUCTION

Norovirus is the predominant cause of gastroenteritis outbreaks worldwide and is responsible for more than 90% of viral gastroenteritis outbreaks [1]. Norovirus is transmitted by several routes, including person-to-person transmission and consumption of contaminated food or water. Prevalence studies in the general population have shown that totally asymptomatic infections may play an important role as the source of infection [2]. The infectious dose for norovirus has been reported to be as low as 18 viral particles [2], and thus norovirus is also one of the main agents responsible for transmission of nosocomial infections between staff and patients/residents [2]. Norovirus can be introduced from the community into healthcare facilities and nursing homes by staff, visitors and patients who might either be incubating or infected with norovirus upon admission [3].

* Author for correspondence: Dr P. Godoy, Head of Epidemiology Unit of Lleida, C/Castell de Farfanya, 12, 25198 Lleida, Spain. (Email: pere.godoy@gencat.cat)
† Other members of the Working Group are listed in the Appendix.

Social changes and an ageing population have, in recent decades, resulted in an increased number of adults with chronic disorders requiring frequent hospitalizations and care in specialized centres [4]. This has facilitated the proliferation of social health centres and assisted-living nursing homes aimed mainly at the elderly. Residents often have a high degree of dependency, which may result in the transmission of nosocomial infections from staff to residents [5]. The risk of nosocomial infection is increased by the degree of dependency and by difficulties in applying preventive protocols due to work overload or insufficient professional training. Therefore, the risk of nosocomial transmission and attack rates could be similar or even higher in hospitals than in nursing homes [2].

Although considered a benign infection, norovirus infections may be severe in the elderly and people with comorbidities and, like influenza infections, have been associated with increased hospitalizations and all-cause deaths [6] during periods of community transmission of the virus.

An increased incidence of outbreaks due to changes in surveillance systems or the appearance of emergent strains has also been reported [7]. Periodic increases in norovirus outbreaks tend to occur in association with new GII.4 strains that evade existing immunity in the community, and may lead to greater transmission in hospitals and nursing homes [7, 8].

The objective of this study was to estimate and compare the incidence of outbreaks of gastroenteritis due to norovirus in hospitals and nursing homes in Catalonia, Spain.

METHODS

A descriptive study of the incidence of norovirus outbreaks between 1 January 2010 and 31 December 2011 in Catalonia, an autonomous community in the northeast of Spain with 7·5 million inhabitants, was performed. In Catalonia, all suspected epidemic outbreaks must be notified to the epidemiological surveillance units (ESUs) of the Department of Health. An outbreak was defined as $\geqslant 2$ cases of gastroenteritis due to norovirus in one centre in a period of 48 h. Patients and healthcare workers met the case definition if they had new onset of vomiting and/or diarrhoea during the outbreak period.

Once a report was received, the ESU confirmed the existence of the outbreak and the clinical and epidemiological characteristics were studied (Fig. 1). Data was collected by ESU staff using a standardized questionnaire. A confirmed case of norovirus gastroenteritis was defined as $\geqslant 2$ loose stools and/or $\geqslant 2$ episodes of vomiting within 24 h and detection of norovirus in faeces. A probable case was defined as a patient with clinical criteria who was epidemiologically related to a confirmed case. The mechanism of transmission was determined through microbiological and statistical analysis for all outbreaks. Epidemiologists, with all the information available, determined the mechanism of transmission for each outbreak and for each patient involved. Therefore, in some outbreaks more than one mechanism of transmission was determined.

An epidemiological survey was made for each outbreak studied, including the following variables: number of people exposed, number of cases, attack rate, mechanism of transmission, type of centre (hospital or nursing home), health region, calendar month and duration. Demographic and clinical information (clinical symptoms, duration of symptoms, transmission mechanism and results of laboratory study of clinical samples) was collected for each case. Clinical samples were collected and shipped to the corresponding reference microbiology laboratory (Public Health Agency Laboratory for the city of Barcelona and the University Hospital Vall d'Hebron Microbiology Laboratory for the other health regions of Catalonia). For each outbreak, all stool samples were investigated if there were fewer than ten cases, and a minimum of ten samples were studied in outbreaks with more than ten cases. Faecal samples were collected during the acute phase (first 3–5 days) of infection; a minimum of 1 *g* stool was collected in a sterile, plastic container without preservative. Stool samples were kept at 4 °C for 2 days and frozen at −20 °C until microbiological analysis, which was performed by the reference laboratories.

Samples were pre-screened using standard microbiological tests to rule out bacteria, parasites, rotaviruses and adenoviruses. Screening for norovirus was performed using two one-step qRT–PCR assays, depending on the laboratory making the analysis. Samples sent to the University Hospital of Vall d'Hebron Microbiology Laboratory were analysed using a duplex qRT–PCR assay based on the primers and hydrolysis probes described by Kageyama *et al.* [9]. Samples sent to the Public Health Agency of Barcelona Laboratory were analysed using the MutaREAL Norovirus Real Time RT–PCR kit (Immundiagnostik, Germany). Genogroups were assigned after amplification by semi-nested RT–PCR of the ORF1/ORF2 junction region (region C), as previously described by Pérez *et al.* [10].

https://doi.org/10.1017/S0950268814001204 Published online by Cambridge University Press

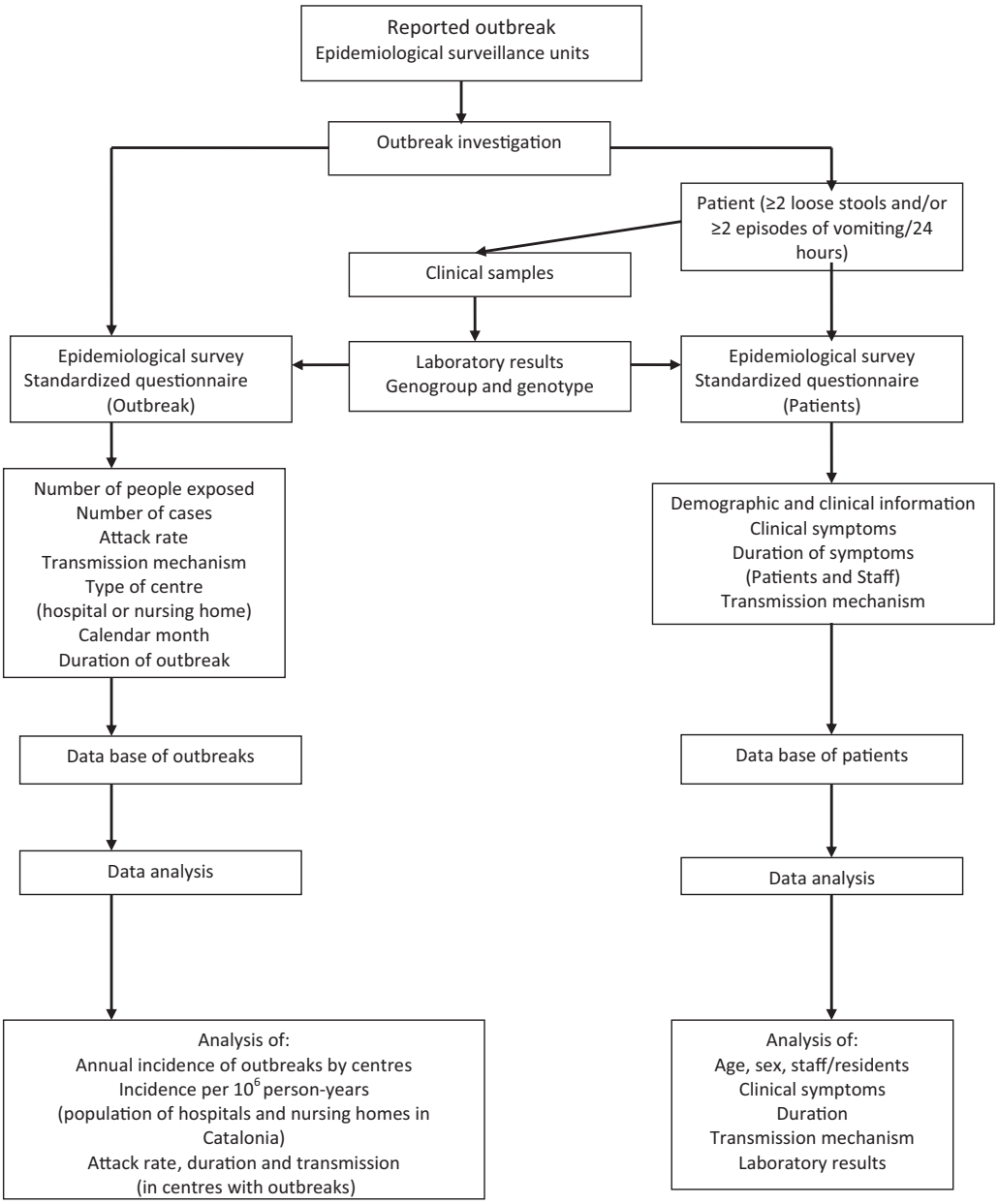

Fig. 1. Protocol scheme of the study of the incidence of norovirus GII.4 outbreaks in hospitals and nursing homes in Catalonia (Spain), 2010–2011.

The annual incidence of outbreaks by centre in a natural year and the incidence/10^6 person-years for the population of hospitals and nursing homes were calculated. The 2011 population and the number of nursing homes and hospitals according to the official 2011 census were used as denominators. We also calculated the attack rate in centres that suffered outbreaks. The 95% CIs were calculated assuming a Poisson distribution. Epidemiological and statistical associations between the dependent variable, [type of centre (hospital or nursing homes)], and the other study variables were determined using ORs and 95% CIs, χ^2 test and Student's t test or Kruskal–Wallis test. The independent effect of each variable was determined using linear regression or logistic regression, as appropriate. Statistical significance was established as $P < 0{\cdot}05$.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the

https://doi.org/10.1017/S0950268814001204 Published online by Cambridge University Press

Table 1. *Incidence, attack rate and duration of norovirus outbreaks in nursing homes and hospitals in Catalonia (Spain), 2010–2011*

	Hospital	Nursing home	Total
Incidence			
Number of centres	247	815	1062
Number of outbreaks	13	14	27
Annual incidence, % (95% CI)	2·6 (1·5–4·4)	0·9 (0·5–1·4)	1·3 (0·9–1·8)
OR (95% CI)	3·2 (1·5–6·9)	1·0 (—)	— (—)
Attack rate			
Patients exposed	995	1353	2348
Cases	371	445	816
Attack rate, % (95% CI)	37·3 (34·3–40·3)	32·9 (30·4–35·4)	34·7 (32·8–36·7)
OR (95% CI)	1·2 (1·0–1·3)	1·0 (—)	— (—)
Duration (days)			
Number of outbreaks	13	14	27
Mean (S.D.)	15·6 (11·3)	13·1 (8·8)	14·3 (10·0)
Median (range)	10·0 (3–34)	10·0 (2–34)	10·0 (2–34)

OR, Odds ratio; CI, confidence interval.

relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

RESULTS

Twenty-seven outbreaks were detected; 13 in hospitals (48·1%) and 14 in nursing homes (51·9%). According to the official census, the incidence of outbreaks in the population of hospitals and nursing homes was 156·6 outbreaks/10^6 person-years. The incidence in all centres in Catalonia was 1·3% per year and was greater in hospitals (2·6%) than in nursing homes (0·9%) (OR 2·6, 95% CI 1·5–2·4) (Table 1). A total of 81·5% (22/27) of outbreaks were due to person-to-person transmission, 11·1% (3/27) were due to foodborne and person-to-person transmission and 7·4% (2/27) were foodborne. Norovirus was confirmed as the agent in all outbreaks.

In centres with outbreaks, 2348 people were exposed, of whom 816 became cases (Table 1). Therefore, the global attack rate was 34·7, and was higher in hospitals than in nursing homes (OR 1·1, 95% CI 1·0–1·2). In addition, there were differences in the attack rate between staff (48·8%, 144/301) and residents of hospitals and nursing homes (32·8%, 672/2047). A total of 17·6% (144/816) of cases occurred in staff, who were advised to cease working until 3 days after recovery from the illness. The mean number of days between the first and last cases of each outbreak was 14·3 (S.D. = 10·0), and was higher in hospitals (mean = 15·6, S.D. = 11·3) than in nursing homes (mean = 13·1, S.D. = 8·8), but the differences were not statistically significant ($P > 0·05$).

Samples were analysed for 358 patients and the results were positive for norovirus in 45%. The most common symptoms were: diarrhoea 61·5%, vomiting 55·0%, abdominal pain 34·9%, nausea 33·8% and fever 20·2% (Table 2). In the bivariate analysis, female sex, younger age group, staff who were patients, person-to-person transmission, nausea, abdominal pain, fever and diarrhoea were more common in hospital patients. The mean duration of symptoms was 2·24 (S.D. = 1·5) days and was greater in hospital patients (2·56, S.D. = 1·7) than in nursing home residents (2·05, S.D. = 1·4) ($P < 0·001$). In the multivariate regression analysis, the $\leqslant 65$ and 65–74 years age groups, staff who were patients, abdominal pain and diarrhoea were associated with hospital patients (Table 3).

There were two deaths, which occurred in females aged 80 and 101 years, respectively. One died in hospital and the other in a nursing home. The case-fatality rate was 0·25% (2/816), but was higher in patients aged $\geqslant 75$ years (0·35%, 2/561).

Most outbreaks (74·1%, 20/27) occurred between December and March (Fig. 2). The genogroup was determined in 55% (15/27) of outbreaks. The most frequent genogroup was GGII, which was found in 86·7% (13/15) of outbreaks. The most frequent genotype was GII.4 which was detected in 66·7% (10/15) of outbreaks. The remaining outbreaks were due to genotypes GII.1, GII.12, GII.6, and GI.7. One outbreak was due to two genotypes (GI.6 and GII.7). The genotypes detected were GII.4 (8/12),

https://doi.org/10.1017/S0950268814001204 Published online by Cambridge University Press

Table 2. *Characteristics of patients with norovirus gastroenteritis in outbreaks in nursing homes and hospitals in Catalonia (Spain), 2010–2011*

	Hospital $N=371$ (%)	Nursing home $N=445$ (%)	OR	95% CI	Total $N=816$ (%)
Gender					
Female	252 (67·9)	335 (75·3)	0·7	0·5–0·9	587 (71·9)
Male	119 (32·1)	110 (24·7)	1·0		229 (28·1)
Age (years)*	66·6 (21·2)	71·6 (21·6)	0·001*		69·8 (21·6)
Age group (years)					
<65	127 (34·3)	69 (15·5)	4·3	3·0–6·3	196 (24·0)
65–74	34 (9·1)	21 (4·8)	3·8	2·1–6·9	55 (6·7)
75–84	116 (31·3)	134 (30·1)	2·0	1·4–2·9	250 (30·6)
⩾85	94 (25·3)	221 (49·7)	1·0		315 (38·6)
Patients					
Staff	84 (22·7)	70 (15·8)	1·6	1·1–2·3	154 (18·9)
Hospital/nursing home patients	287 (77·3)	375 (84·2)	1·0		662 (81·1)
Symptoms					
Diarrhoea	281 (75·8)	221 (49·7)	3·2	2·3–4·2	502 (61·5)
Vomiting	206 (55·5)	243 (54·6)	1·0	0·8–1·4	449 (55·0)
Abdominal pain	175 (47·4)	110 (24·7)	2·7	2·0–3·6	285 (34·9)
Nausea	166 (44·6)	110 (24·6)	2·5	1·8–3·3	276 (33·8)
Fever	91 (24·5)	74 (16·6)	1·6	1·2–2·3	165 (20·2)
Headache	14 (3·8)	14 (3·1)	1·2	0·6–2·6	28 (3·4)
Myalgia	13 (3·5)	23 (5·1)	0·7	0·3–1·3	36 (4·4)
Chills	20 (5·4)	13 (2·8)	1·8	0·9–3·9	33 (4·0)
Transmission					
Person-to-person	317 (85·4)	295 (66·2)	3·0	2·1–4·2	612 (75·0)
Food	54 (14·6)	150 (33·8)	1·0		204 (25·0)
Duration of symptoms (hours) Mean (S.D.)	2·56 (1·7)	2·05 (1·7)	0·001*		2·24 (1·5)
Clinical samples	199/355 (56·1)	211/515 (41·0)	1·8	1·4–2·4	410/870 (47·1)
Positive samples	124/199 (62·3)	141/211 (66·8)	0·5	0·4–0·8	265/410 (64·6)

OR, Odds ratio; CI, confidence interval.
* *P* value for Student's *t* test.

GII.6 (1/12), GI.7 (1/12), GII.12 and GI6–GII.7 (1/12) in the winter months, and GII.4 (2/3) and GII.1 (1/3) in the remaining months.

There were differences between person-to-person and foodborne outbreaks in the attack rate (32·3%, 646/1997 *vs.* 48·4%, 170/351) and the size of the outbreak (mean = 29·4, S.D. = 4·3 *vs.* mean = 34·0, S.D. = 52·2). Genotype GII.4 caused more person-to-person outbreaks (72·7%) than foodborne outbreaks (50%).

DISCUSSION

Our results show that the annual estimated incidence of nosocomial norovirus outbreaks in health centres (1·3%) and in the population of hospitals and nursing homes (156·6 outbreaks/10^6) was very high and was greater in hospitals than in nursing homes. Lopman *et al.* [11] found an incidence of 3–7/10^6 for all types of outbreaks in Europe, including community outbreaks. Surveillance of outbreaks in the USA [12] and Europe [11] show that the incidence, the location and even the seasonality may vary from one year to another. It is unclear whether an increase in outbreaks was due to improved surveillance or to the emergence of new strains. As the same surveillance methods were used throughout this study, it seems likely that the increase and later reduction in outbreaks in Catalonia was due to the emergence of a new strain or to greater seasonal activity of the virus [8, 13]. In addition, the gradual reduction in outbreaks suggests that the population may acquire immunity against the predominant strain [14, 15]. Norovirus transmission and epidemiology has been compared to that of influenza A virus. New antigenic variants of influenza A virus

https://doi.org/10.1017/S0950268814001204 Published online by Cambridge University Press

Table 3. *Variables associated with hospital patients with norovirus gastroenteritis in outbreaks in nursing homes and hospitals in Catalonia (Spain) in the multivariate regression analysis, 2010–2011*

	B	S.E.	Sig.	aOR	95% CI
Gender					
Female	−0·480	0·356	0·177	0·6	0·3–1·2
Male				1·0	
Age group (years)					
<65	3·128	0·628	0·000	22·8	6·7–78·2
65–74	2·225	0·631	0·000	9·2	2·7–31·9
75–84	1·219	0·941	0·195	3·4	0·5–21·4
⩾85				1·0	
Patients					
Staff	−1·796	0·677	0·008	0·2	0·1–0·6
Hospital/nursing home patients				1·0	
Symptoms					
Diarrhoea	1·179	0·355	0·001	3·2	1·6–6·5
Vomiting	−0·102	0·319	0·749	0·9	0·5–1·7
Abdominal pain	0·952	0·345	0·006	2·6	1·3–5·1
Nausea	0·492	0·364	0·177	1·6	0·8–3·3
Fever	0·101	0·421	0·810	1·1	0·5–2·5
Headache	0·204	0·835	0·807	1·2	0·2–6·3
Myalgia	−3·023	1·098	0·006	0·1	0·0–0·4
Chills	1·209	0·920	0·189	3·3	0·5–20·3
Transmission					
Person-to-person	0·298	0·357	0·404	1·3	0·7–2·7
Food				1·0	
Duration of symptoms (hours)	−0·088	0·098	0·367	0·9	0·8–1·1

aOR, Adjusted odds ratio in the multivariate regression model according to the variable in the table; CI, confidence interval.

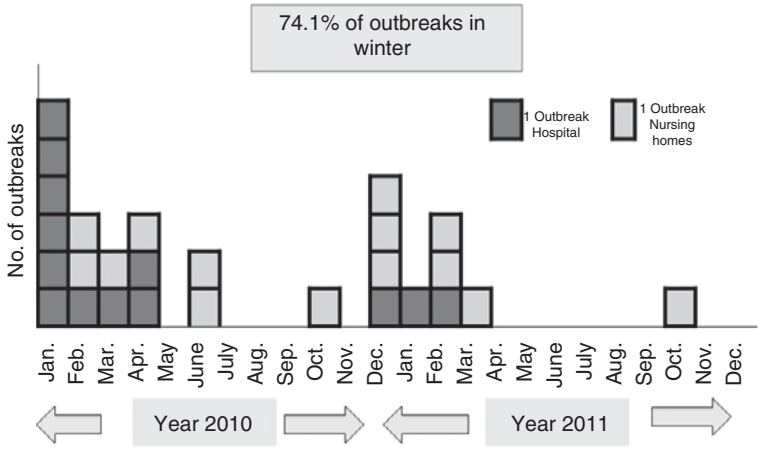

Fig. 2. Outbreaks of norovirus in hospitals and nursing homes in Catalonia ($n=27$), 2010–2011.

emerge every 2–4 years and are associated with epidemics of infection [2, 16–19]. In comparison, pandemic variants of norovirus GII.4 emerged in 2002, 2004, 2006, 2009 and 2012 [2, 16–19].

As in other studies in nursing homes and health centres, most outbreaks were due to GII.4 [7, 20, 21], which is the most common genotype in Europe and has been associated with highly recombinant emergent strains [22] and with an increase in outbreaks in hospitals and nursing homes [21, 22]. Most outbreaks occurred between December and March: this implies a greater risk of transmission during the cold months

https://doi.org/10.1017/S0950268814001204 Published online by Cambridge University Press

due to the greater risk of hospitalization of the elderly and because elderly people tend to spend more time indoors, which may result in greater overcrowding.

The mean duration of symptoms was only 2·24 days, but was longer in hospital patients than in residents of nursing homes. In addition, some symptoms (abdominal pain and diarrhoea) were more frequent in hospital patients in the multivariate analysis. Other studies also have found greater severity and length of symptoms in patients affected by other processes [23]. As in other nosocomial outbreaks, healthcare workers were also affected and, as they had to stop work until 3 days after recovering, this resulted in significant loss of income and increased use of resources [24, 25].

Most outbreaks were caused by person-to-person transmission and, once a centre was affected, the final attack rates were high (34·7%), showing the difficulty of controlling transmission due to the diversity of transmission mechanisms [26, 27] and low compliance with hand washing [28]. The incidence of outbreaks and the attack rates were higher in hospitals than in nursing homes, suggesting that transmission of the virus may be greater in hospitals and that nosocomial infection protocols may be more difficult to apply. No significant differences were observed in the duration of outbreaks in the two types of centres and the global duration was similar to that observed by Harris *et al*. [29] in a systematic review of the duration of outbreaks in centres with control measures, both documented and undocumented (16 *vs*. 14 days). The attack rate of 34·7% observed was in the high range of the rates found by a systematic review of outbreaks by Matthews *et al.* [21], which estimated a rate of 27% (95% CI 12–46) in person-to-person outbreaks and 20% (95% CI 6–34) in outbreaks in health centres. It has been reported that elderly people with comorbidities shed a greater amount of the virus and for a longer time and this would facilitate not only the transmission but also the longer duration of outbreaks [21, 30, 31].

The mortality rate was 0·25%, which was similar to that observed by other studies. A review of reported outbreaks by Desai *et al*. [32] found a mortality rate of 0·39% in health centres. More recently, a study of the surveillance of outbreaks due to the new emerging strain by Leshem *et al*. [13] found a mortality rate of 0·2–0·4%. A cohort study by Trivedi *et al*. in nursing homes affected by outbreaks [6] found the risk of death was 1·14 times higher in the outbreak period compared to periods without outbreaks ($P<0·001$).

The main strength of this study is that it documents the importance of norovirus outbreaks in Catalonia according to incidence by centre, the population at risk in hospitals and nursing homes and the attack rate in the centres affected. Notably, all outbreaks were confirmed microbiologically, clinical samples were available from a large number of patients and all outbreaks were investigated by the same experienced epidemiological staff using the same protocol.

The study has some limitations. Due to the mildness of the symptoms and the clinical course of the disease, some outbreaks may not have been detected. In addition, outbreaks due to person-to-person transmission are less likely to be detected than those due to other types of transmission and might have been underdetected. However, most outbreaks studied were due to person-to-person transmission. The validity of the symptoms and duration of the clinical course could be questioned in some elderly people with cognitive disorders, especially residents of nursing homes. Similarly, the intensity and duration of symptoms might be less evident in hospitalized patients due to the more-intensive treatment administered. Therefore, the differences found between hospital patients and nursing home residents might also have been underestimated.

CONCLUSIONS

The incidence of norovirus outbreaks in hospitals and nursing homes in Catalonia was very high and was associated with significant mortality. Most outbreaks were caused by genotype GII.4 and were due to person-to-person transmission. The significant disruption of patient care and the cost of nosocomial outbreaks support aggressive efforts to prevent norovirus transmission in healthcare settings and nursing homes [26–28]. Primary control measures of norovirus outbreaks, such as environmental decontamination with solutions of hypochlorite at 1000–5000 ppm, the prevention of food contamination, the exclusion of sick workers, the cohorting of infectious patients and ensuring hand washing or the use of alcoholic solutions among healthcare workers, should be improved [2, 27].

APPENDIX

The other members of the Working Group for the Study of Outbreaks of Acute Gastroenteritis in Catalonia are:

M. Alsedà, J. Alvarez, C. Arias, A. Artigues, I. Barrabeig, P. J Balanyà, N. Camps, M. Company,

https://doi.org/10.1017/S0950268814001204 Published online by Cambridge University Press

M. Carol, G. Ferrús, N. Follia, A. Martínez, S. Minguell, I. Parrón, A. Rovira, M.R. Sala, N. Torner, R. Torra, J. Torres (Public Health Agency of Catalonia. Barcelona, Spain), M. de Simón, D. Ferrer, A. Moreno, M. Sanz (Public Health Agency of Barcelona, Barcelona, Spain), R. Bartolomé, T. Cornejo (Microbiology Department. University Hospital Vall d'Hebron. Barcelona, Spain), A. Bosch, S. Guix, R Pintó (Enteric Virus Department. University of Barcelona, Barcelona, Spain) and S Broner (CIBER Epidemiology and Public Health, CIBERESP, Spain).

ACKNOWLEDGEMENTS

This project was funded by Instituto de Salud Carlos III (FIS PS0902516 and CIBERESP) and the Catalan Agency for the Management of Grants for University Research (AGAUR Grant no. 2009/SGR 42).

DECLARATION OF INTEREST

None.

REFERENCES

1. **Patel MM, *et al.*** Noroviruses: a comprehensive review. *Journal of Clinical Virology* 2009; **44**: 1–8.
2. **Hall AJ, *et al.*** Updated norovirus outbreak management and disease prevention guidelines. *Morbidity and Mortality Weekly Report* 2011; **60**: 1–12.
3. **Mattner F, *et al.*** Evaluation of the impact of the source (patient versus staff) on nosocomial norovirus outbreak severity. *Infection Control and Hospital Epidemiology* 2005; **26**: 268–272.
4. **Godoy P, *et al.*** Norovirus gastroenteritis outbreak by person-to-person transmission in a nursing home. *Medicina Clínica* 2006, **127**: 538–541.
5. **Lopman B, *et al.*** Institutional risk factors for outbreaks of nosocomial gastroenteritis: survival analysis of a cohort of hospital units in South-west England, 2002–2003. *Journal of Hospital Infection* 2005; **60**: 135–143.
6. **Trivedi TK, *et al.*** Hospitalizations and mortality associated with norovirus outbreaks in nursing homes, 2009–2010. *Journal of the American Medical Association* 2012; **308**: 1668–1675.
7. **Svraka S, *et al.*** Etiological role of viruses in outbreaks of acute gastroenteritis in the Netherlands from 1994 through 2005. *Journal of Clinical Microbiology* 2007; **45**: 1389–1394.
8. **Zheng D, *et al.*** Molecular epidemiology of genogroup II-genotype 4 noroviruses in the United States between 1994 and 2006. *Journal of Clinical Microbiology* 2010; **48**: 168–177.
9. **Kageyama T, *et al.*** Broadly reactive and highly sensitive assay for Norwalk-like viruses based on real-time quantitative reverse transcription-PCR. *Journal of Clinical Microbiology* 2003; **41**: 1548–1557.
10. **Pérez U, *et al.*** Human norovirus occurrence and diversity in the Llobregat river catchment, Spain. *Environmental Microbiology* 2012; **14**: 494–502.
11. **Lopman B, *et al.*** Viral gastroenteritis outbreaks in Europe, 1995–2000. *Emerging Infectious Diseases* 2003; **36**: 90–96.
12. **Hall AJ, *et al.*** Norovirus disease in the United States. *Emerging Infectious Diseases* 2013; **19**: 1198–1205.
13. **Leshem E, *et al.*** Effects and clinical significance of GII. 4 Sydney norovirus, United States, 2012–2013. *Emerging Infectious Diseases* 2013; **19**: 1231–1238.
14. **Lindesmith LC, *et al.*** Mechanisms of GII. 4 norovirus persistence in human populations. *PLoS Medicine* 2008; **5**: e31.
15. **Cannon JL, *et al.*** Herd immunity to GII. 4 noroviruses is supported by outbreak patient sera. *Journal of Virology* 2009; **83**: 5363–5374.
16. **Bull RA, *et al.*** Emergence of a new norovirus genotype II. 4 variant associated with global outbreaks of gastroenteritis. *Journal of Clinical Microbiology* 2006, **44**: 327–333.
17. **Tu ET, *et al.*** Norovirus GII. 4 strains and outbreaks, Australia. *Emerging Infectious Diseases* 2007; **13**: 1128.
18. **Tu ET, *et al.*** Epidemics of gastroenteritis during 2006 were associated with the spread of norovirus GII. 4 variants 2006a and 2006b. *Clinical Infectious Diseases* 2008; **46**: 413–420.
19. **Fonager J, Barzinci S, Fischer T.** Emergence of a new recombinant Sydney 2012 norovirus variant in Denmark, 26 December 2012 to 22 March 2013. *Eurosurveillance* 2013; **18**: 2–7.
20. **Blanton LH, *et al.*** Molecular and epidemiologic trends of caliciviruses associated with outbreaks of acute gastroenteritis in the United States, 2000–2004. *Journal of Infectious Diseases* 2006; **193**: 413–421.
21. **Matthews J, *et al.*** The epidemiology of published norovirus outbreaks: a review of risk factors associated with attack rate and genogroup. *Epidemiology & Infection* 2012; **140**: 1161–1172.
22. **Siebenga JJ, *et al.*** Gastroenteritis caused by norovirus GGII. 4, the Netherlands, 1994–2005. *Emerging Infectious Diseases* 2007; **13**: 144.
23. **Lopman BA, *et al.*** Clinical manifestation of norovirus gastroenteritis in health care settings. *Clinical Infectious Diseases* 2004; **39**: 318–324.
24. **Johnston CP, *et al.*** Outbreak management and implications of a nosocomial norovirus outbreak. *Clinical Infectious Diseases* 2007; **45**: 534–540.
25. **Lopman BA, *et al.*** Epidemiology and cost of nosocomial gastroenteritis, Avon, England, 2002–2003. *Emerging Infectious Diseases* 2004; **10**: 1827.
26. **Wu HM, *et al.*** A norovirus outbreak at a long-term-care facility: the role of environmental surface

contamination. *Infection Control and Hospital Epidemiology* 2005; **26**: 802–810.

27. **Weber DJ, *et al.*** Role of hospital surfaces in the transmission of emerging health care-associated pathogens: norovirus, Clostridium difficile, and Acinetobacter species. *American Journal of Infection Control* 2010; **38**: S25–S33.
28. **Cooper E, Blamey S.** A norovirus gastroenteritis epidemic in a long-term-care facility. *Infection Control and Hospital Epidemiology* 2005; **26**: 256–258.
29. **Harris J, Lopman B, O'Brien S.** Infection control measures for norovirus: a systematic review of outbreaks in semi-enclosed settings. *Journal of Hospital Infection* 2010; **74**: 1–9.
30. **Rockx B, *et al.*** Natural history of human calicivirus infection: a prospective cohort study. *Clinical Infectious Diseases* 2002; **35**: 246–253.
31. **Cieslak P, *et al.*** Recurring norovirus outbreaks in a long-term residential treatment facility-Oregon, 2007. *Morbidity and Mortality Weekly Report* 2009; **58**: 694–698.
32. **Desai R, *et al.*** Severe outcomes are associated with genogroup 2 genotype 4 norovirus outbreaks: a systematic literature review. *Clinical Infectious Diseases* 2012; **55**: 189–193.